

What is claimed is:

1. A method of identifying a compound that modulates premature translation termination or nonsense-mediated mRNA decay, said method comprising:

- 5 (a) contacting a member of a library of compounds with a cell containing a first nucleic acid sequence and a second nucleic acid sequence, wherein the first nucleic acid sequence comprises a regulatory element operably linked to a reporter gene and the second nucleic acid sequence comprises a nucleotide sequence with a premature stop codon that encodes a regulatory protein that binds to the regulatory element of the first nucleic acid sequence and
10 regulates the expression of the reporter gene; and
- (b) detecting the expression of the reporter gene, wherein a compound that modulates premature translation termination or nonsense-mediated mRNA decay is identified if the expression of the reporter gene in the presence of the compound is altered relative to the expression of the reporter gene in the
15 absence of the compound or the presence of a negative control.

2. A method of identifying a compound that modulates premature translation termination or nonsense-mediated mRNA decay, said method comprising:

- 20 (a) contacting a member of a library of compounds with a cell containing a first nucleic acid sequence, a second nucleic acid sequence and a third nucleic acid sequence, wherein (i) the first nucleic acid sequence comprises a nucleotide sequence encoding a first fusion protein comprising a DNA binding domain and a first protein, the nucleotide sequence of the first protein containing a premature stop codon, (ii) the second nucleic acid sequence comprises a nucleotide sequence encoding a second fusion protein
25 comprising an activation domain and a second protein, the second protein interacting with the first protein to produce a regulatory protein, and (iii) the third nucleic acid sequence comprises a regulatory element operably linked to a reporter gene, the expression of the reporter gene being regulated by the binding of the regulatory protein to the regulatory element; and
- 30 (b) detecting the expression of the reporter gene, wherein a compound that modulates premature translation termination or nonsense-mediated mRNA decay is identified if the expression of the reporter gene in the presence of

the compound is altered relative to the expression of the reporter gene in the absence of the compound or the presence of a negative control.

3. A method of identifying a compound that modulates premature translation termination or nonsense-mediated mRNA decay, said method comprising:

- 5 (a) contacting a member of a library of compounds with a cell containing a first nucleic acid sequence, a second nucleic acid sequence and a third nucleic acid sequence, wherein (i) the first nucleic acid sequence comprises a nucleotide sequence encoding a first fusion protein comprising a DNA binding domain and a first protein, (ii) the second nucleic acid sequence
- 10 comprises a nucleotide sequence encoding a second fusion protein comprising an activation domain and a second protein, the nucleotide sequence of the second protein containing a premature stop codon and the second protein interacting with the first protein to produce a regulatory protein, and (iii) the third nucleic acid sequence comprises a regulatory
- 15 element operably linked to a reporter gene, the expression of the reporter gene being regulated by the binding of the regulatory protein to the regulatory element; and
- (b) detecting the expression of the reporter gene, wherein a compound that modulates premature translation termination or nonsense-mediated mRNA
- 20 decay is identified if the expression of the reporter gene in the presence of the compound is altered relative to the expression of the reporter gene in the absence of the compound or the presence of a negative control.

4. A method for identifying a compound that modulates premature translation termination or nonsense-mediated mRNA decay, said method comprising:

- 25 (a) contacting a member of a library of compounds with a cell-free translation mixture and a nucleic acid sequence comprising a regulatory element operably linked to a reporter gene, wherein the reporter gene contains a premature stop codon and the cell-free translation mixture is isolated from cells that have been incubated at about 0°C to about 10°C; and
- 30 (b) detecting the expression of the reporter gene, wherein a compound that modulates premature translation termination or nonsense-mediated mRNA decay is identified if the expression of the reporter gene in the presence of

the compound is altered relative to the expression of the reporter gene in the absence of the compound or the presence of a negative control.

5. A method for identifying a compound that modulates premature translation termination or nonsense-mediated mRNA decay, said method comprising:

- 5 (a) contacting a member of a library of compounds with a cell-free translation mixture and a nucleic acid sequence comprising a regulatory element operably linked to a reporter gene, wherein the reporter gene contains a premature stop codon and the cell-free translation mixture is a S10 to S30 cell-free extract; and
- 10 (b) detecting the expression of the reporter gene, wherein a compound that modulates premature translation termination or nonsense-mediated mRNA decay is identified if the expression of the reporter gene in the presence of the compound is altered relative to the expression of the reporter gene in the absence of the compound or the presence of a negative control.

15 6. The method of claim 4, wherein the cell-free translation mixture is a S10 to S30 cell-free extract.

7. The method of claim 5, wherein the cell-free translation mixture is a S12 cell-free extract.

20 8. The method of claim 6, wherein the cell-free translation mixture is a S12 cell-free extract.

9. A method of identifying a compound to be tested for its ability to prevent or treat a disease characterized by or associated with the presence of a premature stop codon in a gene, said method comprising:

25 (a) contacting a member of a library of compounds with a cell containing a nucleic acid sequence comprising a reporter gene with a premature stop codon; and

(b) detecting the expression of the reporter gene,

so that if the expression of the reporter gene in the presence of the compound is altered relative to the expression of the reporter gene in the absence of the compound or the

presence of a negative control, then a compound to be tested for its ability to prevent or treat the disease is identified, wherein the disease is familial hypercholesterolemia, osteogenesis imperfecta, cirrhosis, ataxia telangiectasia or a lysosomal storage disease.

10. A method of identifying a compound to be tested for its ability to prevent or
5 treat a disease characterized by or associated with the presence of a premature stop codon in a gene, said method comprising:

- (a) contacting a member of a library of compounds with a cell-free translation mixture and a nucleic acid sequence comprising a reporter gene with a premature stop codon; and
- 10 (b) detecting the expression of the reporter gene,

so that if the expression of the reporter gene in the presence of the compound is altered relative to the expression of the reporter gene in the absence of the compound or the presence of a negative control, then a compound to be tested for its ability to prevent or treat the disease is identified, wherein the disease is familial hypercholesterolemia, osteogenesis
15 imperfecta, cirrhosis, ataxia telangiectasia or a lysosomal storage disease.

11. The method of claim 1, 2, 3, 4 or 5, wherein the method further comprises determining the structure of the compound that suppresses premature translation termination or nonsense-mediated mRNA decay.

12. The method of claim 9 or 10, wherein the method further comprises
20 determining the structure of the compound.

13. The method of claim 1, 2, 3, 4, 5, 9 or 10, wherein the reporter gene is firefly luciferase, renilla luciferase, click beetle luciferase, green fluorescent protein, yellow fluorescent protein, red fluorescent protein, cyan fluorescent protein, blue fluorescent protein, beta galactosidase, beta glucuronidase, beta lactamase, chloramphenicol
25 acetyltransferase, or alkaline phosphatase.

14. The method of claim 1, 2, 3 or 9, wherein the cell is selected from the group consisting of 293T, HeLa, MCF7, Wi-38, SkBr3, Jurkat, CEM, THP1, 3T3, and Raw264.7 cells.

15. The method of claim 4, 5 or 10, wherein the cell-free translation mixture is a cell-free extract from 293T, HeLa, MCF7, Wi-38, SkBr3, Jurkat, CEM, THP1, 3T3, or Raw264.7 cells.

5 16. The method of claim 1, 2, 3, 4, 5, 9 or 10, wherein the compound is selected from a combinatorial library of compounds comprising peptoids; random biooligomers; diversomers such as hydantoins, benzodiazepines and dipeptides; vinylogous polypeptides; nonpeptidal peptidomimetics; oligocarbamates; peptidyl phosphonates; peptide nucleic acid libraries; antibody libraries; carbohydrate libraries; and small organic molecule libraries.

10 17. The method of claim 16, wherein the small organic molecule libraries are libraries of benzodiazepines, isoprenoids, thiazolidinones, metathiazanones, pyrrolidines, morpholino compounds, or diazepindiones.

18. The method of claim 1, 2, 3, 4, 5, 9 or 10, wherein the premature stop codon is UAG or UGA.

15 19. The method of claim 1, 2, 3, 4, 5, 9 or 10, wherein the premature stop codon context is UAGA, UAGC, UAGG, UAGU, UGAA, UGAC, UGAG or UGAU.